# Heart Failure

## Introduction and Review

Heart failure, also known as congestive heart failure (CHF), is the common end stage of many forms of chronic heart disease, often developing insidiously from the cumulative effects of chronic work overload or ischemic heart disease. CHF occurs when the heart is unable to pump blood at a rate sufficient to meet the metabolic demands of the systemic tissues. In short, heart failure occurs when cardiac output becomes compromised sufficiently to maintain a sufficient perfusion pressure, i.e., MAP. That systemic vascular resistance is the enemy of cardiac output cannot be overstated. The normal, healthy response to a compromised MAP **is the cause** of the eventual failure. What **was compensatory** is **now pathologic**. As the body demands more from the heart ($\beta_1$ stimulation, calcium conductance, myocardial work), it also demands more from the vasculature (increases SVR, afterload), which in turn makes the heart work even harder. This vicious cycle leads the heart to compete with the systemic vascular resistance.

We begin with a discussion of the ~~MAP~~ work equation, previewing the lesson's outcome—equating the original stress to the type of cardiac myocyte remodeling (concentric or eccentric hypertrophy) and to the overall ventricular remodeling (preserved ejection fraction vs. reduced ejection fraction). We then detail ventricular remodeling and ventricle and cardiac myocyte responses to stress, compare the clinical presentation of left and right heart failure, and close with systolic and diastolic heart failure.

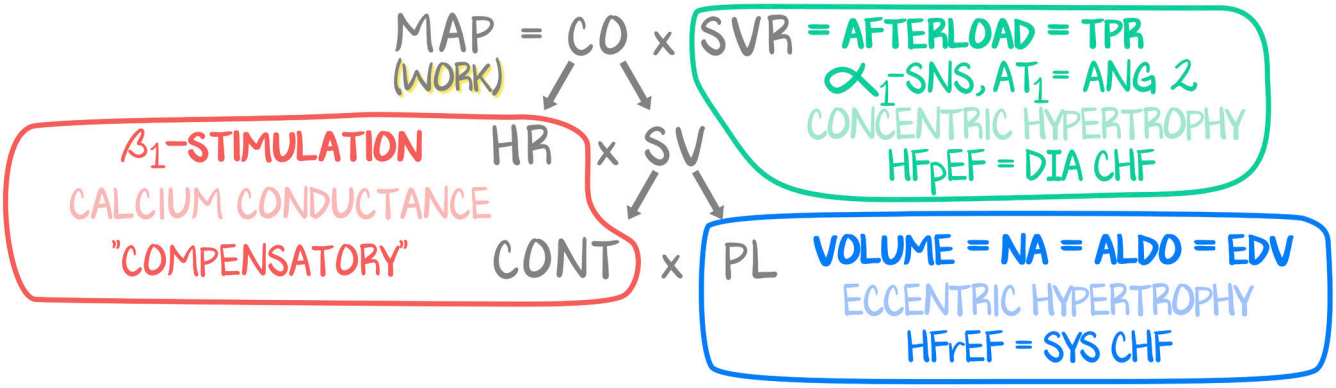


**Figure 6.1: The MAP Equation**
See this equation in Heart Failure Land as fitting into three possible categories: $\beta_1$ as what drives the heart and induces the signal to grow, preload as the insult that leads to eccentric hypertrophy, and afterload as the insult that leads to concentric hypertrophy.

## Ventricular Remodeling

The above adaptive mechanisms – increasing heart rate and contractility —may be adequate to maintain normal function in the face of acute perturbations, but their capacity to do so is ultimately overwhelmed because of superimposed pathologic changes within the heart itself. The myocytes attempt to adapt to increased stress, but ultimately respond the wrong way, leading to failure. The collective molecular, cellular, and structural changes that occur as a response to stress are called **ventricular remodeling**. We go into the details of ventricular modeling and the ventricular response to stress, then turn to the cellular response to stress. All are interrelated, but the story told in each section varies slightly.

## Ventricular Response to Stress

The ventricle will always hypertrophy in response to stress, driven by $\beta_1$ stimulation. How it hypertrophies varies dependent upon a second stressor – usually excess preload or excess afterload. To a clinical pathologist, **hypertrophy** means a **heavier heart**. The heart gets bigger and therefore weighs more. This distinction is important because it does not necessarily mean a stronger heart. There are two ways the heart gets bigger, corresponding to the initial insult: concentric hypertrophy from increased afterload, and eccentric hypertrophy from increased preload. Hypertrophy is initiated by stimulation of $\beta_1$ receptors. The insult determines the expression of various genes.

In pressure-overload hypertrophy (e.g., due to hypertension or aortic stenosis), which you should equate with afterload-overload hypertrophy in accordance with the MAP equation, new sarcomeres are assembled in parallel (to the side of existing sarcomeres), making the myocytes bigger in the transverse axis. Myocytes get stronger, but at the cost of being fatter. Fatter myocytes lead to **concentric hypertrophy**—fatter myocytes, fatter ventricular wall. Concentric hypertrophy is a stronger heart. It can beat harder—it overcomes the resistance, the pressure that stimulated these changes. But a fatter ventricular wall means less space to accept blood, and the heart becomes stiff. Strong, capable of expelling blood, but stiff, incapable of accepting blood. This results in **impaired ventricular filling**, which is a different way of saying **diastolic dysfunction**. When the cause is felt equally on all sides by the ventricle (as in hypertensive heart and aortic stenosis, by far the most common causes of concentric hypertrophy), the changes are also felt equally around the ventricle. Thus, there is a concentric (all the way around equally) concentric hypertrophy (sarcomeres added in parallel, or side by side).

In contrast, volume-overload hypertrophy (aortic valve insufficiency, ischemic heart disease, impaired ejection fraction) is characterized by new sarcomeres being assembled in series (at the ends of existing sarcomeres), making the myocytes bigger in the longitudinal axis. Myocytes get longer. Longer myocytes means **eccentric hypertrophy**—longer myocytes, bigger chamber. A bigger chamber is dilation. A longer ventricle is, at first, a stronger ventricle. Dilating too far, it becomes a weaker ventricle. It has no problem accepting blood, but has trouble expelling blood. Thus there is no impaired filling, but there is an **impaired ejection fraction**, which is another way of saying **systolic dysfunction**.

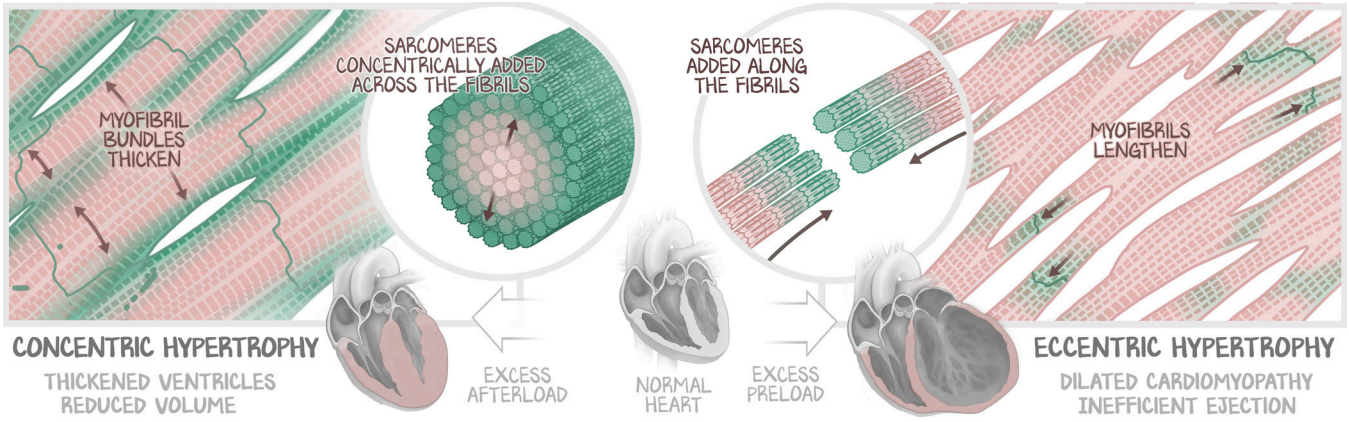


**Figure 6.2: Ventricular Hypertrophy**
$\beta_1$ receptor activation acts as a trophic signal for cardiac myocytes. If the cardiac myocytes are induced to hypertrophy and the stress is afterload, there will be a concentric hypertrophy, with sarcomeres added in parallel, making the cardiac myocytes fatter and wider, leading to a bigger, beefier, and stiff ventricle. If the cardiac myocytes are induced to hypertrophy and the stress is preload, there will be an eccentric hypertrophy, with sarcomeres added in series, marking the cardiac myocytes longer and thinner, leading to a dilated, misshapen ventricle.

Outside the heart, the body is still responding to maintain MAP. Sympathetics and RAAS are active. The continued $\beta_1$ stimulation acts as a trophic signal as well as increases calcium conductance. Myocytes hypertrophy. RAAS causes sustained increase in mechanical work through increased preload through aldosterone. Stretch alters gene expression. Eccentric hypertrophy is induced by excess stretch. Sustained $\alpha_1$ stimulation and Ang 2 stimulation increase systemic vascular resistance. Pressure overload against myocytes changes gene expression. Concentric hypertrophy is induced by excess afterload.

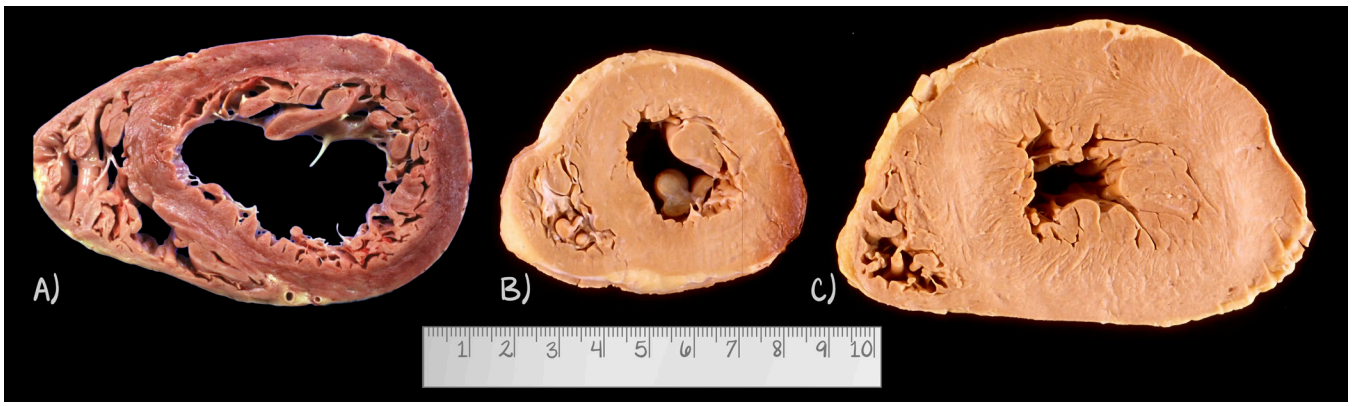


**Figure 6.3: Ventricular Response to Stress**
These are three hearts, cross-sectioned at approximately the same level. The heart to the left of normal has a huge lumen, the ventricular wall is almost normal thickness, but the entire ventricle has been dilated. This sample is taken from a patient with dilated cardiomyopathy, where both the left and right ventricles are dilated. This is eccentric hypertrophy. The heart to the right of normal was taken from a patient with severe aortic stenosis (increased afterload) demonstrating a narrowed lumen and significantly widened ventricular wall. This is concentric hypertrophy.

## Cellular Response to Stress

Myocyte hypertrophy is the addition of sarcomeres. Additional sarcomeres, additional contractile units, additional force of contraction, and force of contraction is interchangeable with additional work. This adaptation is positive in both concentric and eccentric hypertrophy. At least in the beginning. The heart has not failed yet, merely begun to adapt to whatever stress is applied.

But oh, wait, additional sarcomeres, additional ATP demands, additional oxygen demands. Myocyte remodeling—the addition of sarcomeres—occurs within myocytes. There aren't any signals to nearby capillaries that the oxygen demands are going up. That means myocyte hypertrophy is **not accompanied by an increase in capillaries**. So, the myocytes have additional oxygen demands, but no additional oxygen supply, putting them at higher risk for hypoxemia, for ischemia.

Hypertrophy is also often accompanied by deposition of fibrous tissue called interstitial fibrosis. Fibrosis is scar. Interstitial fibrosis means that between the cardiac myocytes on a histology slide from a patient with heart failure (whether it be concentric or eccentric) will appear evidence of cellular loss and the replacement of those cells with fibrosis. So where does that fibrosis come from?

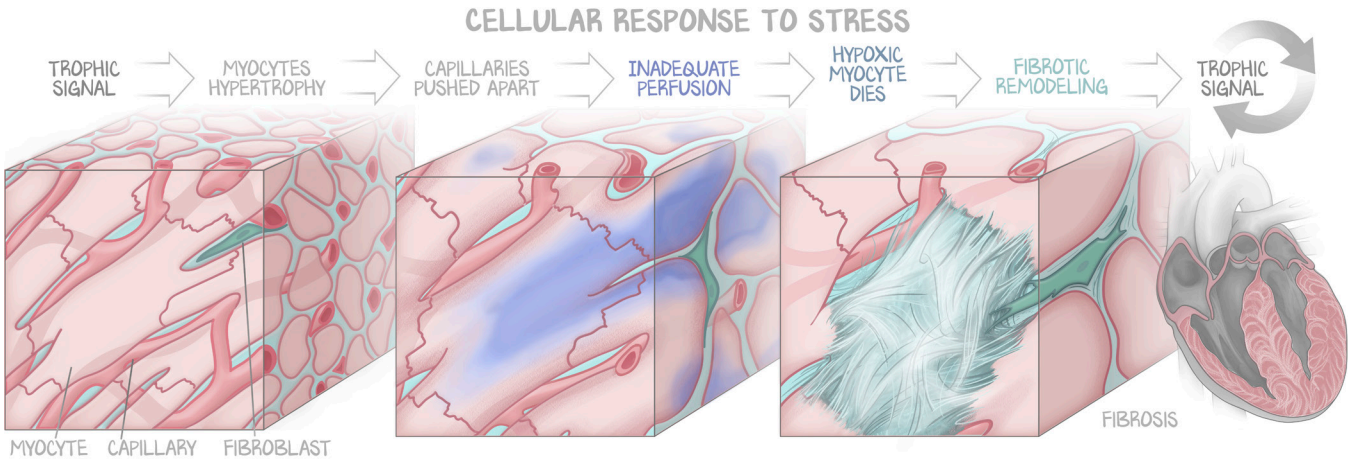


**Figure 6.4: Cellular Response to Stress**
In response to $\beta_1$ stimulation, myocytes hypertrophy. Whether concentric or eccentric, the myocytes get larger, have more sarcomeres, and have a larger force of contraction but also an increased myocardial oxygen demand. There is not a compensatory increase in capillaries, in the delivery of blood, to match the myocyte hypertrophy. This is not akin to a heart attack—the perfusing vessels are normal, but simply fail to carry enough blood for the hypertrophied cardiac myocytes. Slowly, they die off, and the space they occupied is replaced by fibrosis.

That sustained increased-demand-without-increased-supply leads to alteration of gene expression in myocytes, then to apoptosis, and eventually to fibrosis. The **cellular progression to failure** occurs gradually. Stress is applied to all cells at once. As one, myocytes build out their sarcomeres, maintaining cardiac output. They build their sarcomeres to accommodate whatever stress has been applied. In addition, while responding to this stress, the rest of the body is demanding more from them. The myocytes, while handling this stress, are also being whipped by the sympathetic nervous system. They all get bigger together. The whipping gets them working harder, adding even more sarcomeres. They all get stronger together. But then some of their friends start disappearing. And we're not talking a bomb going off, taking out a city block (that would be necrosis, a myocardial infarction, with neutrophils, macrophages, fibroblasts). We're talking one at a time, little by little. One by one, myocytes throw in the towel. The group doesn't really notice when one falls—it was just one myocyte. But with the loss of that one, the rest must work harder. Progressively, more and more myocytes tap out, and the rest are left to deal with the burden. So they get bigger, get stronger together—the survivors, anyway. The ones that are left have increased work, increased demand, but no accompanying increase in capillaries. Where those myocytes die off, fibrosis replaces them, the heart unable to regenerate, being a $G_0$ tissue.

## The Two-Heart Model and CHF Symptoms

Whatever its etiology, whatever the resultant morphology (see Systolic vs. Diastolic Dysfunction, below), CHF is manifested by a combination of the inability to pump blood forward to tissues (**forward failure**) and by the backup of blood into the veins (**backward failure**). As a result, the clinical manifestations of heart failure will be signs of tissue hypoxia in front of the heart and congestion behind the heart.

**When the pump breaks, it can't pump blood forward to where the blood needs to go.**

**When the pump breaks, blood builds up behind the broken pump.**

There are two hearts: a right heart and a left heart. There are two pumps: a right ventricle and a left ventricle. There are two syndromes: right heart failure and left heart failure. They can occur together. In fact, the most common cause of right heart failure is left heart failure, and you will look for both of them to complete the syndrome of "heart failure." When right heart failure occurs independently, it gets a special name – cor pulmonale (isolated right heart failure from increased pulmonary artery pressures).

Despite their interdependence, you must separate them as independent from one another. Why? An acute myocardial infarction of the left ventricle will present with left heart failure symptoms only, and a massive pulmonary embolism will present with right heart failure symptoms only.

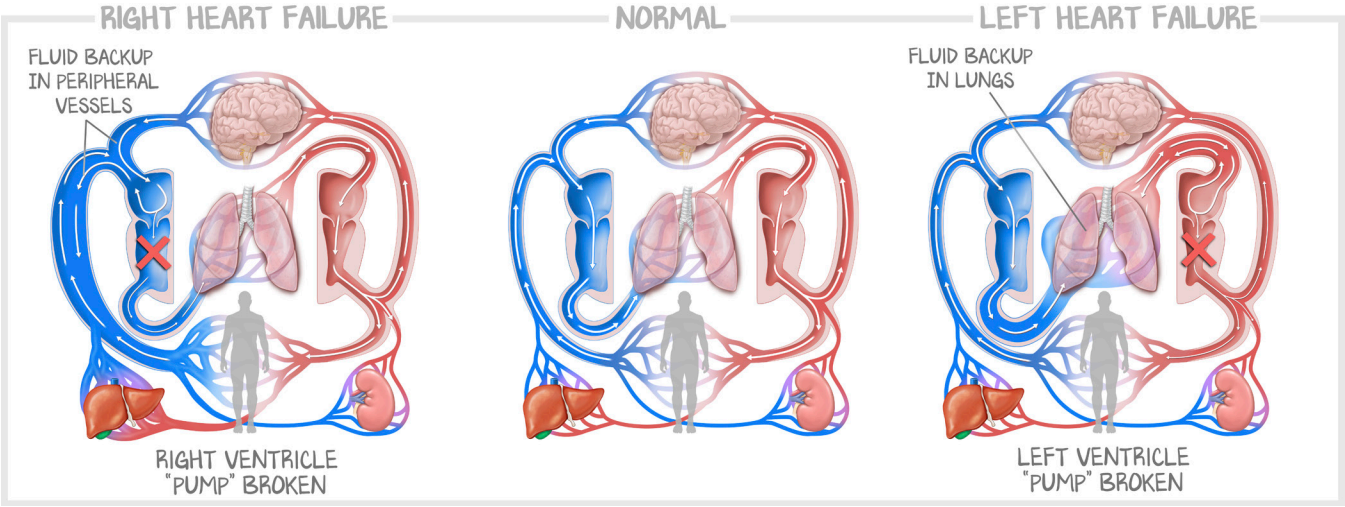


**Figure 6.5: The Two-Heart Model**
The right ventricle receives blood from the superior and inferior vena cava. The right ventricle then pumps blood into the pulmonary vasculature. If this pump breaks, blood will back up before the broken pump, in the vena cava. If this pump breaks, the left side cannot receive oxygenated blood, and will present with hypoxemia. The left ventricle receives blood from the pulmonary veins and pumps it into the systemic vasculature. If this pump breaks, blood will back up before the broken pump, in the lungs. If this pump breaks, the systemic tissues will not be well perfused, and will present with hypoxemia.

## Left Pump Failure

In left pump failure, the blood backs up into the lungs. The backup of blood leads to an increased capillary hydrostatic pressure, and fluid is forced out of the capillaries into tissues. This fluid is within the alveoli of the lungs. First, in the septa, then into the alveoli. Left pump failure results in pulmonary symptoms, pulmonary physical exam findings, and pulmonary imaging.

**Pulmonary symptoms.** Fluid in the alveolar septae and in the alveolar spaces is pulmonary edema. Pulmonary edema presents with **dyspnea** (shortness of breath). The degree of pulmonary edema determines the severity of dyspnea. A little bit of fluid in the lungs causes mild **exertional dyspnea** (shortness of breath with exertion). As the fluid continues to accumulate, the amount of activity and the duration it can be sustained decreases. The wetter a patient becomes, the worse their limitations. **Paroxysmal nocturnal dyspnea** (PND) is the sensation of dyspnea that awakens the patient from sleep, who then often rushes to a window, fan, or refrigerator (all things that alleviate the sensation of dyspnea). What has actually happened is that fluid in the alveoli layered out during sleep, affecting more alveoli and worsening the impaired oxygen exchange. Standing up allowed gravity to pool the fluid down to the base of the lungs, minimizing the total alveoli affected. PND is associated with **orthopnea**, the sensation of dyspnea while lying flat. The more fluid there is, the less flat the patient can be. Patients may describe propping themselves up with more and more pillows to avoid symptoms at night, even sitting upright in a chair. The findings of **exertional dyspnea**, **orthopnea**, and **PND** together have a positive likelihood ratio for left ventricular CHF that is better than a troponin is for a heart attack. The absence of all three has a negative likelihood ratio so good that the negative history alone rules out heart failure.

**Physical exam findings.** The pulmonary findings of left heart failure are **rales**, "wet crackles." The patient is usually upright (because being supine causes orthopnea), so the fluid will be best heard at the base of the lungs. Crackles that clear with coughing are atelectasis. Crackles that do not clear with a forceful cough are

likely fluid. If a pleural effusion is present, there will be reduced lung sounds, dullness to percussion, and decreased fremitus. The ventricular sounds and point of maximal impulse are different based on etiology (systolic or diastolic). Systolic failure with reduced ejection fraction will have a displaced PMI and an S3. Diastolic failure and volume overload will present with an S4. They are discussed below.

**Imaging.** Chest X-ray and POCUS can reliably estimate the amount of volume overload. The smallest amount of volume overload is indicated by the engorged pulmonary venous markings called Kerley B lines. As more fluid accumulates in the alveoli, dependent pulmonary edema is seen. The next to fill are the pulmonary fissures, especially visible on the right, without the heart to obscure them. The most severe is a pleural effusion. But do not be fooled—the fluid in the pleural cavity is not connected to the fluid in the alveoli—it is merely a marker of more and ongoing fluid accumulation.

**Pathology.** With the increased hydrostatic pressure in the veins of the lungs, the fluid is a transudate. Yet small congested capillaries leak so much that red cells and plasma proteins extravasate into the alveolar space. Macrophages gobble them up, and store the iron from the red blood cells as hemosiderin. **Hemosiderin-laden macrophages** are also known as **heart failure cells**. You won't have difficulty identifying the patient with volume overload and pulmonary edema, but you may be asked to look at a biopsy of a lung and be asked to define the pathology without the clinical context. Hemosiderin-laden macrophages mean pulmonary edema due to heart failure.

## Right Pump Failure

**Signs and symptoms.** When the right pump breaks, fluid backs up into the two venae cavae. In the superior vena cava, that excess buildup of fluid is visualized in the internal jugular vein. **Jugular venous distension** (JVD) is an elevated jugular venous pulsation. The presence of visible jugular venous pulsations above the collarbone in any position other than supine is pathological. In the inferior vena cava, that buildup of fluid goes two places. The first major vein distal to the inferior vena cava is the hepatic vein. Venous congestion causes **hepatomegaly**. The hydrostatic forces push fluid out of capillaries. This occurs most forcefully near the central veins, resulting in congested red-brown pericentral zones, with normal-colored tan periportal regions, producing the **nutmeg liver**. Gravity pulls fluid down. Excess volume in the inferior vena cava exerts increased hydrostatic pressures on the capillaries and venules of the dependent regions. This presents with **peripheral edema**. Excess volume can be detected before symptoms arise by daily tracking of body weight. **Weight gain** is the earliest sign of volume overload.

The original studies that ranked peripheral edema as 1+, 2+, 3+, and 4+ used those numbers to refer to the time of pit recovery and were used to predict the albumin. Nowadays, "3+ pitting edema" has various meanings. Some people use it to refer to the severity of edema (the circumference). Some people use it to refer to the height of edema (how high up the leg). Almost no one uses it the way it was intended—pit recovery occurred in under 90 seconds, which implies that this is a hydrostatic edema. Get into the habit now of being purposefully descriptive with edema, and do not use the 1+ method, as it now is impossible to interpret someone else's use of the number. Say instead, "there is a severe amount of edema at the ankles, with modest amount of edema above the knee. It is pitting with a pit recovery time of under 30 seconds."

**Laboratory diagnosis.** The right ventricle is broken. Fluid backs up before the broken ventricle. Notice the change from pump to ventricle? The thing before the broken right ventricle is the right atrium. When the right atrium is stretched, it releases **atrial natriuretic peptide (ANP)**. This is the heart's only mechanism to tell everyone else there's a problem. No one listens, except the kidney. ANP signals volume overload and induces afferent arteriolar vasodilation, which improves GFR, and then induces a natriuresis in the kidneys. It filters more sodium, then eliminates more sodium. ANP, therefore, acts to directly oppose aldosterone and angiotensin 2, leading to a loss of volume through the kidneys. While aldosterone is busy bringing in excess volume (via sodium from collecting ducts), exacerbating the excess

preload, ANP is putting up a fight. ANP induces diuresis (loss of sodium means loss of volume) in the kidneys. The RAAS signal is louder, and wins.

**Brain natriuretic peptide** (BNP), first discovered in the brain, is the laboratory value that reflects ANP and atrial stretch. If the BNP is below 200, volume overload is not present. If the BNP is above 500, volume overload is present.

## Systolic vs. Diastolic Dysfunction

The heart muscle does two things: contract and relax. When the problem is deficient contraction, the action the heart muscle makes in systole, it is called systolic dysfunction. When the problem is deficient relaxation, the action the heart muscle does in diastole, it is called diastolic dysfunction.

**Systolic dysfunction** is defined by a **reduced ejection fraction**. In heart-failure language, systolic dysfunction disorders are called "Heart Failure with a reduced Ejection Fraction" (HFrEF). The heart cannot pump blood forward because it has an impaired contractility. Ejection fraction is compromised by **leaky hearts** (valvular regurgitation allows the ejected blood to go the wrong way in systole), **floppy hearts** (dilated cardiomyopathy), and **dead hearts** (myocardial infarction). Leaky, floppy, and dead. This is different than in the ventricular response to stress. Systolic dysfunction may be due to volume-overload-induced eccentric hypertrophy, but it does not have to be. Systolic dysfunction presents with an **S3 heart sound** and often a **laterally, inferiorly displaced PMI**.

An S3 heart sound is caused by increased ventricular compliance. It is heard only with the bell of the stethoscope, with patient in left lateral decubitus, the stethoscope at the point of maximal impulse. If you haven't heard an S3, it is because you haven't first palpated the PMI, turned the patient on their left side, and listened with the bell. S3 occurs immediately after S2.

**Diastolic dysfunctions** come from a stiff, rigid ventricle that refuses to budge during diastolic filling. The stroke volume is not impaired. The ejection fraction is normal. In heart-failure language, diastolic dysfunction disorders are called "Heart Failure with a preserved Ejection Fraction" (HFpEF). This is not the same thing as concentric hypertrophy—the heart weighs more because the ventricle is thicker. Hypertensive heart disease results in a concentric (all the way around) concentric hypertrophy (sarcomeres added in parallel), but very often is. Diastolic dysfunction and hypertensive heart disease are so closely related that they are often taught as the same thing. But there may be diastolic dysfunction from other causes (as discussed in *Cardiomyopathy*). However, in all cases, the lumen of the chamber narrows as the muscle takes up more space. There is **impaired diastolic filling** with an **increase in ventricle pressure** at smaller end-diastolic volumes. Diastolic dysfunction produces an **S4 heart sound**.

An S4 heart sound is caused by increased ventricular stiffness. It is caused when an already high-pressure, stiff ventricle receives atrial kick. Atrial contraction occurs immediately before ventricular contraction, just before the mitral valve closes, **just before S1**. As the ventricle is already full of blood, it is noncompliant at high pressures at lower end-diastolic volume, and the atrial contraction's striking of the ventricle is what generates the sound.

A memory tool for S3 vs. S4 is this. Since systolic failure can't get all the blood out, when the mitral valve opens, the incoming blood plops into the left-over blood. That plop is S3, and it occurs immediately after the mitral valve opens. Whereas S4 is because the ventricle is too stiff, and the atria have to push really hard to get that last bit of blood in the chamber. The pressures are so high that the mitral valve closes briefly, is pushed on by the atrium, and then closes again for real with ventricular contraction. This makes teleologic sense, but is not what actually happens.

Other causes of dysfunction are discussed in Structure and Function #8: *Cardiomyopathy*.